IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Tsuyoshi NAGANUMA et al

Application No.: 10/538,514 Confirmation No.: 1878

Filed: June 9, 2005 Group Art Unit: 4133

For: SOLID DRUG FOR ORAL USE

Examiner: Walter E. Webb

DECLARATION UNDER 37 C.F.R 1.132

Honorable Commissioner for Patents

Washington, D.C. 20231

Sir:

I, Tsuyoshi NAGANUMA of 4622-38, Toyoshina, Azumino-shi, Nagano 399-8205 JAPAN, being duly sworn, declare and state:

THAT I am by profession a research chemist having a bachelor's degree in industrial chemistry from Chuo University in March 1990.

THAT I have been employed since April 1990 by Kissei Pharmaceutical Co., Ltd. of 19-48, Yoshino, Matsumoto-shi, Nagano 399-8710 JAPAN and engaged in engineering and research mainly on:

production on drug products in the production department of the same company from April 1990 to September 1990; and then

formulation technology studies on drug products in Central Research Laboratories of the same company from October 1990 up to now.

THAT I am one of co-inventors of the invention disclosed in the above-identified U.S. patent application and hence I am fully familiar therewith.

In order to demonstarate that the present invention is unobvious over Ishihara, we have conducted the following experiment for comparing the capsule of the present invention with a capsule suggested by Ishihara.

Experiment

1. Preparation of capsules of example 1 and comparative capsule

Example 1

In accordance with the procedures as described in Example 1 on page 34 in the present specification, a capsule of exmple 1 was preparaed as follows.

A mixture of KMD-3213 (320g), D-mannitol (21,504g), partially pregelatinized starch (PCS, 4,160g) and partially pregelatinized starch (Starch 1500, 1,440g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. A mixture of magnesium stearate (288g) and sodium lauryl sulfate (288g) was added thereto, mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 2.0mg of KMD-3213.

In preparing the capsules of exmple 1, no filling troubles was observed during encapsulating process, and good manufacturing aptitude was achieved.

Comparative capsule

Ishihara discloses tablets of formulation examples 1 to 6 in the specification. All the tablets contain lactose, corn starch and magnesium stearate. On the contrary, the results of compability test shown in Table 2 in the present specification indicate that lactose generates degradation products twice as large as D-mannitol. We believe that there is no motivation to combine the teaching of the tablets of formulation examples 1 to 6 in Ishihara with the capsules of the present invention. Whilst Ishihara describes general mentions regarding dosage forms including capsule; and bulking agent including D-mannitol in the specification.

In order to compare the dissolution rate of the capsule of the present invention with a formulation that may be suggested by Ishihara, we have prepared a comparative capsule using mannitol instead of lactose acoording to the tablet of Formulation example 1 as described on page 51 of US2002/0177593 as follows. Since D-mannitol is the most suitable ingredient for a filler as desclibed on page 26, lines 4 to 5 in the specification, the comparative capsule has a composition more similar to the capsule of the present invention as compared with the tablets disclosed in Ishihara.

A mixture of KMD-3213 (216.2 g), D-mannitol (7,687 g) and corn starch (1,922 g) were mixed sufficiently. Separately, corn starch (78.24 g) was suspended in water (2,172.8 g), and the suspension was heated at about 80 °C to prepare starch paste. The mixture was granulated with the starch paste. The granule was dried using a fluid bed drier at an inlet air temperature of about 60 °C until the exhaust air reaches 40 °C, and sieved. Magnesium stearate (97.3 g) was added to the sieved granules and mixed for 10 minutes, and the mixture was filled

into a capsule shell to prepare a capsule containing 4.0mg of KMD-3213.

In preparing the comparative capsules, significant adhering onto tamping pin of an encapsulator was observed during encapsulating process.

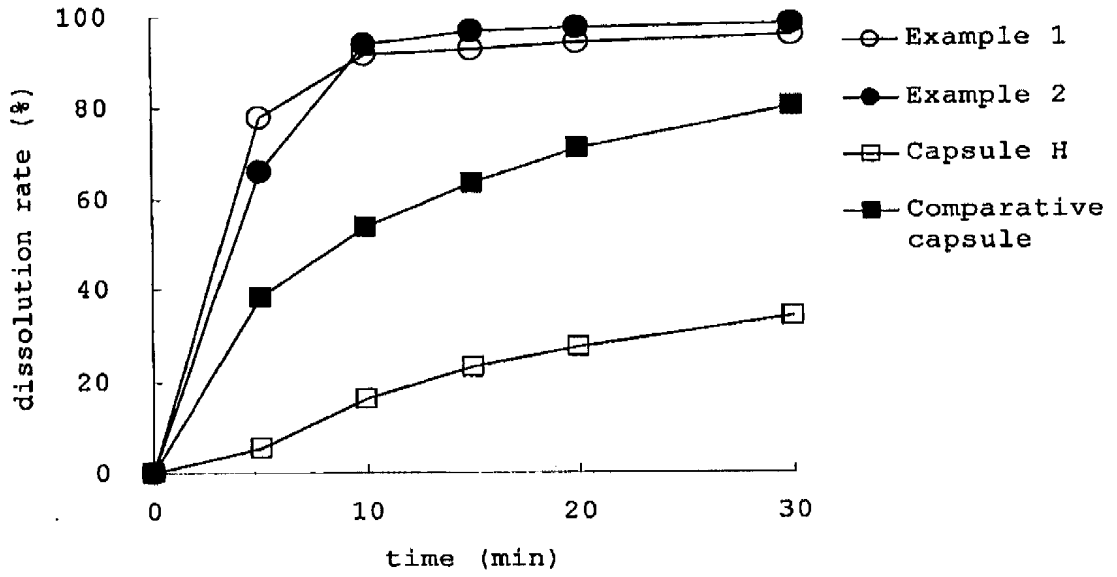
2. Dissolution test

In accordance with the procedures of "Dissolution Test Method" as described in Test example 4 in the present specification, the capsules of example 1 and 2 of the present invention; the comparative capsules as prepared above; and formulation H as described in Table 5 in the present formulation were tested. Their dissolution rates are shown in Drawing 1.

Table 1

Capsule	Example 1	Example 2	Capsule H	Copamparative capsule
KMD-3213	2.0	4.0	2.0	4.0
D-Mannitol	134.4	132.4	134.4	142.2
Partially pregelatinized starch (PCS)	26.0	26.0	26.0	
Partially pregelatinized starch (Starch 1500)	9.0	9.0	9.0	
Corn starch				37
Magnesium stearate	1.8	1.8	1.8	1.8
Sodium Lauryl Sulfate	1.8	1.8		
total weight (mg/capsule)	175.0	175.0	173.2	185

Drawing 1



The results of dissolution tests show clearly that the capsules of the present invention have much higher dissolution rate as compared with those of the comparative capsule and Capsule H. During encapsulating process of the comparative capsule, filling troubles of sticking were observed, whereas no filling trouble was noted for the capsules of the present invention. Such advantageous effects of the capsule of the present invention cannot be predicted from the teaching of Ishihara.

Therefore, we believe that the capsule of the present invention is unobvious over Ishihara.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

March 26, 2008

Tsuyoshi Naganuma.

Tsuyoshi NAGANUMA